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Published in:
EBioMedicine

DOI:
[10.1016/j.ebiom.2017.04.021](https://doi.org/10.1016/j.ebiom.2017.04.021)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Huckriede, A. (2017). Immunoglobulin Infusion as Therapy Against Influenza? *EBioMedicine*, 19, 10-11.
<https://doi.org/10.1016/j.ebiom.2017.04.021>

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Commentary

Immunoglobulin Infusion as Therapy Against Influenza?



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With about 3–5 million severe cases and 250,000–500,000 deaths yearly, seasonal influenza infections form a constant and serious threat to the human population (*Influenza (Seasonal) Fact sheet*, n.d.). In addition, new influenza virus strains, often originating in birds or pigs, may cross the species barrier to humans and cause pandemics with potentially very high attack rates and sometimes high mortality (Trombetta et al., 2015). While vaccination can protect from seasonal influenza strains it will be of limited use in the first months of a pandemic since vaccine production and distribution will lag behind as experienced during the Swine Flu in 2009. Antivirals can provide an outcome and in fact have been stockpiled by several countries as a first line of defence in case of a pandemic. Yet, influenza virus appears to rapidly acquire resistance against antivirals. Thus, new intervention options are urgently needed.

Intravenous immunoglobulin (IVIg) preparations consist of pooled serum IgG fractions from several thousand individuals. Originally employed as replacement therapy for immunodeficient individuals, IVIg is currently recognized as an immunomodulating intervention suitable for treatment of a variety of autoimmune, infectious and idiopathic diseases (Scheinfeld, 2016). IVIg has been used sporadically for treatment of influenza patients, mainly with the idea that the preparation will contain influenza-specific antibodies which can interfere with the infecting virus. Indeed, influenza-specific antibodies with broad specificity have been found in IVIg preparations and proved to mediate antibody-dependent cellular cytotoxicity (ADCC) *in vitro* (Jegaskanda et al., 2014).

In this issue of *EBioMedicine*, Rockman and co-workers report on a study into the *in vivo* effects of IVIg therapy using ferrets as a well-established animal model for influenza (Rockman et al., 2017—in this issue). The study demonstrates that IVIg preparations from before 2009 have the capacity to ameliorate disease symptoms in ferrets infected with 2009 H1N1pdm virus, and protect from death caused by infection with lethal H5N1 virus. Thus, IVIg preparations provided protection although they did not contain antibodies elicited by the challenge viruses. This is an important observation which implies that IVIg can be used as treatment option for newly emerging virus strains.

In a series of well-designed experiments the authors tried to unravel the mechanism of action of IVIg *in vivo*. They observed that the

protective effect was independent of virus-neutralizing, hemagglutination-inhibiting and neuraminidase-specific antibodies. Even when pre-absorbed with influenza virus, IVIg still had protective activity. F(ab')₂ fragments were equally potent as entire antibodies while Fc fragments were inactive. This indicates that the antigen binding region of the antibodies is important for the protective effect. Moreover, protection by F(ab')₂ fragments alone rules out the possibility, at least in this model, that mechanisms relying on complement activation, ADCC or antibody-dependent phagocytosis (ADP) are crucial for the observed protection. Also, induction of anti-inflammatory IL10 could be ruled out as an essential mechanism. Thus, despite all the attempts made the authors could not reveal how IVIg affords protection against influenza infection. They speculate that low levels of cross-reactive antibodies present in IVIg preparation might be responsible for the observed effects.

With many of the 'usual suspects' eliminated what else could explain the effect of IVIg on influenza infection and course of disease? Studies into possible targets of IVIg antibodies have revealed among others anaphylatoxins and cytokines which would be in line with an anti-inflammatory effect of IVIg [reviewed in (Schwab and Nimmerjahn, 2013)]. Indeed, preclinical and clinical studies emphasize that treatment of influenza infections with anti-inflammatory drugs can mitigate disease symptoms without having an effect on lung virus titers (Howard et al., 2011). Furthermore, IVIg preparations have been shown to contain large amounts of carbohydrate-binding antibodies (van Gunten et al., 2009). As influenza virus uses sialic acid residues on membrane glycoproteins of epithelial cells as a receptor, carbohydrate-binding antibodies may shield receptor binding sites of the virus thus preventing cellular infection.

Sialic acid residues might also play a role in another way. IgG preparations contain large amounts of sialylated antibodies and recent studies have demonstrated that these are crucial for the anti-inflammatory effects of IVIg [reviewed in (Schwab and Nimmerjahn, 2014)]. Both the F(ab')₂ part as well as the Fc part of the antibodies can contain sialic acid residues. Yet, while the immunosuppressive role of sialylation of the Fc part is undisputed, data on the role of sialylation of the F(ab')₂ part for anti-inflammatory effects is less clear. Sialylated F(ab')₂ parts may, however, have yet another function. A recent study indicates that they can serve as decoy receptors for influenza virus thus preventing binding of the virus to its target cells (Huang et al., 2013).

Even though the precise mechanism of action remains elusive evidence has accumulated that IVIg might be an effective therapy for severe influenza. A big asset is that IVIg preparations are readily available and IVIg therapy is already well established in the clinic. On

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2017.04.010>.

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the downside, large amounts of antibodies are required for the antiviral effect, making use of IVIg as widespread therapy difficult and expensive. Moreover, the therapy needs to start as early as possible after infection for maximal effectiveness. Given the fact that flu-like symptoms are very common for a range of infections, early detection of influenza-infected individuals might be difficult. However, with a further improved understanding of how IVIg exerts its anti-influenza effects it might be possible to develop more effective preparations. In addition, rapid influenza diagnostic tests can help in the early detection of infected individuals to expedite the start of treatment for maximal therapeutic effect.

Conflict of Interest

The author declares no conflicts of interest.

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